Remarks

Claims 17-20 are pending in the application. Claim 19 has been amended to provide proper antecedent basis, support for which may be found on page 21, lines 12-25 and in Example 1 starting on page 44. Claims 21-36 are new. Exemplary support for certain of the new claims may be found, for example and without limitation, as follows:

Claim 17: page 34, line 11-12.

Claims 21-24: page 10, lines 19-23 and in the Examples.

Claims 25-26: page 33, line 21 through page 32, line 21 and Examples 2 through 12.

Claim 27: page 35, line 25 through page 36, line 23 and Example 4.

Claim 28: page 40 lines 15-34 and Example 12.

Claim 29: page 36, line 25 through page 37, line 30 and Examples 7, 9, 10, and 11.

Claim 30: page 16 line 8 through page 19, line 36 and the Examples.

Claim 31: page 16 line 8 through page 19, line 36.

Claim 32: page 16 line 8 through page 19, line 36 and the Examples.

Claim 33: page 4, lines 14-21, page 5, lines 30-36, page 19, lines 24-30 and the claims as originally filed.

Claims 34-35: page 33, line 21 through page 32, line 21 and Examples 2 through 12.

Claim 36: page 16, lines 29-25.

Additional support for the amendments to the claims may be found throughout the specification, including the originally filed claims. *No new matter has been added.* Any amendments to and/or cancellation of the claims was done solely to more particularly point out and distinctly claim the subject matter of Applicants' invention in order to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Continued Examination Under 37 C.F.R. 1.114

Applicants thank the Examiner for granting Applicants' request for continued examination and entering Applicants' submission and for withdrawing the finality of the previous Office Action.

Rejection of claims 17-20 under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 17-20 under 35 U.S.C. § 112, first paragraph alleging that the specification, while being enabling for a method specific for the p21 as the bioactive agent that modulates a specific tumor cell, does not reasonably provide enablement for a method using a library of any bioactive agents that modulates any population of cells. The Examiner alleges that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicants respectfully traverse this rejection.

Specifically, the Examiner alleges that the scope of enabling disclosure in the specification is not commensurate in scope with the recited method, which "employs broadly any type of library of bioactive agent that affects any type of cell population" and that "the exemplification is drawn to a single bioactive agent, p21, for a particular type of cell population, tumor."

Applicants respectfully direct the Examiner's attention to M.P.E.P. § 2164.01, which cites *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989). "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." Further, Applicants also respectfully direct the Examiner's attention to M.P.E.P. § 2164.02, which states in relevant part: "[t]he presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure, even though it is a factor to be considered along with all the other factors. To make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims."

Applicants note that the express purpose of the present invention is to evaluate *whether or not a candidate bioactive agent alters a cellular phenotype by* introducing it into the cells via a retroviral vector or by combining the cells with it, and *analyzing the cells for phenotypic changes via at least five FACS parameters*. The Examples serve to demonstrate proof of principle whereby a candidate bioactive agent (i.e., p21) was tested using the method of the invention to determine whether or not it alters the phenotype of the cells into which it was introduced, as detected by at least five FACS parameters. The intention of selecting p21 as the "candidate bioactive agent" was that its properties as a cell-cycle inhibitor (see page 16, lines 14-15) were known and expected to produce the phenotypic changes detected by the parameters described in Examples 1-12, as proof that the instantly claimed invention works, e.g. that at least five FACS parameters could be used to detect the phenotypic changes in a cell retrovirally transfected with a bioactive agent. Indeed, the changes in cellular phenotype induced by the p21, which was introduced via a retroviral vector into Jurkat, MC-9 cells and RBL-2H3 cells, were successfully analyzed using at least five different parameters using FACS analysis (e.g., as outlined in Examples 1 through 12). These Examples demonstrate, therefore, that if a bioactive agent is transfected into a cell using a retroviral vector, changes in the cell's phenotype that result may be successfully analyzed via at least five parameters, using FACS analysis.

The specification provides ample guidance as to how the teachings of the Examples may be modified for use in other cell types using other candidate bioactive agents. Applicants remind the Examiner that "the purpose of the [enablement] requirement that the specification describe the invention in such terms that one skilled in the art can make and use the claimed invention is to ensure that the invention is communicated to the interested public in a meaningful way. The information contained in the disclosure of an application must be sufficient to inform those skilled in the relevant art how to both make and use the claimed invention. Detailed procedures for making and using the invention may not be necessary if the description of the invention itself is sufficient to permit those skilled in the art to make and use the invention." (M.P.E.P. § 2164)

First, contrary to the Examiner's assertion that the recited method "employs broadly any type of library of bioactive agent that affects any type of cell population, " Applicants invention is limited to "a population of cells comprising a *library of retroviral vectors* encoding different candidate bioactive agents" wherein the cells are retrovirally infectable. Applicants have amended claim 17 to require that the cells be "retrovirally infectable" to clarify that the types of

cells to be used in the method must be infectable with a retroviral vector. Methods of introducing agents using retroviral vectors into a variety of retrovirally infectable cell types were well-known in the art at the priority date of the present application. The Examples provide guidance for transfecting three different cell types with a retroviral vector encoding p21. Preparing a library of cells infected with different candidate bioactive agents would involve the same technique, which would be simply repeated for each cell to be transfected with a different bioactive agent, until a plurality (or library) of cells each having different agents retrovirally transfected into them was produced. Further, the specification provides further guidance for those elements specifically discussed in the Examples. Ample guidance for selecting and preparing libraries of candidate bioactive agents is provided, for example and without limitation, at page 16, line 8 through page 19, line 37. Ample guidance for incorporating such libraries of agents into retroviral vectors is provided, for example and without limitation, at page 19, line 35-36, page 20, line 1-page 21, line 11 and by reference to the PCT applications page 20 line 3-4. Further, cells that are retrovirally infectable or not were well-known in the art at the priority date of the invention. Moreover, the application provides a list of exemplary retrovirally infectable cells, see, e.g., page 34, lines 11-17. Still further, ample guidance as to FACS analysis of various phenotypes using various parameters, over and beyond what is provided in the Examples, is provided starting, for example, at page 31, line 16 through page 44, line 29. Considering the number of working Examples, the amount of guidance in the specification and the level of skill in the art, it would not require undue experimentation to modify the methods of the instant application to use other retrovirally infectable cell types and other candidate bioactive agents.

Applicants further disagree with the Examiner's contention on page 4 of the Office Action that "[t]he specification fails to give adequate direction and guidance in how to readily go about determining the bioactive agent(s) present in a library of unknown compounds, whether said bioactive agents present in the library are identical or different, the number of said bioactive agents comprise in the library, the method of screening or determining as whether a bioactive agent is a candidate for cell population reaction, the size of the library comprising a different bioactive agent, the altering effect of the bioactive agents on the phenotype of the cell population, the type of cell population that can be altered by a bioactive agent, the more than five different parameters that can be measured by FACS and other unpredictable effects." All of these determinations are well within the ordinary level of skill of one skilled in the art, even if no

guidance were provided in the specification. One of skill in the art would know that a library of bioactive agents will contain a heterogeneous group of compounds (hence the term "library"). If one of skill in the art prepared a library, counting the number of its members would be well within that person's skill. For example, preparing a library of cells infected with different candidate bioactive agents could involve the same technique as disclosed in the Examples and specification, which could be simply repeated for each cell to be transfected with a different bioactive agent from the library, until a plurality (or "library") of cells each having different agents retrovirally transfected into them, was produced. It is within the skill of one of skill in the art to determine the identity of a bioactive agent in a cell, for example, by isolating the genetic material and via PCR amplifying the relevant material which may be submitted for nucleotide sequence analysis, thus identifying the agent. In embodiments where the library is added exogenously to the cells as in new claim 34, those cells which exhibit an altered cellular phenotype could be, for example, cross-referenced with the agent added. As noted above, the specification provides ample guidance as to all of these issues, as does the ordinary skill in the art.

As to the "unpredictability" of the effect of the agents on the phenotype of the cell, or the "screening or determining as whether a bioactive agent is a candidate for cell population reaction," the *point* of the invention is to determine what the effect of each agent is on the cell. Thus, these points are irrelevant to the enablement analysis. Applicants strongly urge the Examiner, as we urged in our previous response to the prior Office Action, that the Patent Office has recognized screening assay claims having no limitation as to the compounds to be tested (see, e.g., U.S. Patent No. 6,461,813) and that this invention should be similarly treated.

The Examiner on page 5 of the Office Action objects to Applicants' alleged failure to provide working examples for any library of bioactive agents or nucleic acids in any retroviral vector transfected into any organism i.e. viruses, yeast or bacteria. As noted above, the specification (as well as the level of skill in the art) provides ample guidance for infecting any retrovirally infectable cell with the retroviral vectors of the invention.

The Examiner contends in point 3 on page 5 that "the consequences of some bioactive agents and cell interaction on some cells have not been fully determined or elucidated." Applicants agree with the Examiner and submit that this point underscores the purpose of the

current invention. More specifically, the function of the methods of the present invention is to determine the effect of such compounds on cellular phenotypes.

Further, the Examiner contends in point 4 on page 5 that "the art is inherently unpredictable" with respect to various aspects of the invention. Applicants remind the Examiner that "the scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required." (M.P.E.P. § 2164.03. Applicants again point out that ample guidance for preparing other species based on the operable species of the examples is provided in the specification and one skilled in the art could do so without undue experimentation.

The Examiner again contends in point 5 on page 6 that "the breadth of the claims encompasses a large possible combination for the different recited variables such as the large diversity of bioactive agents or nucleic acids that encode said bioactive agent and the cell population." Again, Applicants underscore that the point of the invention is to be able to test the effect of a large number of bioactive agents on the phenotype of a variety of cells, and notes that the claims are more specifically directed to retrovirally infectable cells.

The Applicants disagree with the Examiner that it would require undue experimentation to make the invention commensurate in scope with what is claimed based on the guidance and direction provided in the instant application. As outlined above, Applicants submit that ample guidance and direction is provided in the specification to one skilled in the art having the knowledge of one so skilled for the claims, and simply because a large amount of work *might* be required to prepare a library of retroviral vectors in a retrovirally infectable cell type different from those in the Examples does not mean undue experimentation is involved. The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*,

537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). Time and expense are merely factors in this consideration and are not the controlling factors. *Telectronics Inc.*, 857 F.2d at 785, 8 USPQ2d at 1223. Applicants respectfully suggest that the Examiner may be misinterpreting what is simply a routine amount of experimentation as undue experimentation.

In response to the Examiner's comments on page 8 of the office action regarding how the FACS measures the five or more parameters simultaneously on each cell, Applicants wish to draw the Examiner's attention to the measurements being made on each cell outlined in Example 1. The first two parameters measured by the FACS include the physical properties of the cell, namely forward and side scatter. Forward and side scatter measure the size and granularity of the cells respectively, thus allowing one skilled in the art to designate the population of cells to be used for data acquisition. The third parameter measured by the FACS are those cells that are expressing the p21 construct through detection of the GFP fluorescence label on the retrovirus. Simultaneously, the FACS measures all cells due to their uptake of the cell tracker dye, pkh26, in the red channel (as a fourth parameter), and the fifth parameter was the DNA content of the cell as determined by excitation of the Hoechst 33342 dye with the UV-laser. Those cells which are growth arrested remain cell tracker dye bright, while in cycling cells the cell tracker dye is diluted resulting in dim signals. Example 1 thus successfully demonstrates proof of principle regarding the ability of the FACS to allow multiparameter detection of the effect of a compound on a cell's phenotype in relation to cell cycle analysis. Furthermore, any cell type may be used in Applicants' FACS-based assay, since the forward and side scatter parameters could be adjusted for the cell type.

Applicants again disagree with the Examiner's objection on page 9, beginning "[T]o select and determine the various agents that would affect a cell phenotype in five different ways amounts to an invitation to experiment . . . ." As stated in the preceding text, Applicants would again like to stress that it is the objective of the instant invention to identify agents which can affect a cellular phenotype as accessed by FACS. No prior knowledge is needed of the agents - the point is to test whether or not they would affect a cellular phenotype. The Examiner mischaracterizes Applicants' invention by saying that the agents must "affect a cell phenotype in five different ways." Rather, five different parameters are used to determine whether the agent affects the cellular phenotype.

Applicants conclude that the disclosure in the specification is sufficient to allow one of skill in the art to practice the claimed invention without undue experimentation, because the nature of the invention is a screening method to determine whether libraries of compounds have an effect on a cell's phenotype, the state of the art in retroviral transfection and FACS analysis was well-established at the time of filing, and Applicants have provided multiple working examples as well as ample guidance in the specification. Accordingly, Applicants respectfully request withdrawal of the present rejection.

Rejection of claims 17-20 under Double Patenting

The Examiner has rejected claims 17-20 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 5 of Application No. 09/157,748 (now U.S. Patent No. 6,461,813) or over application S.N. 09/062,330 for reasons of record.

Applicants respectfully traverse the foregoing rejection. However, at such time as the subject matter of the instant application is indicated allowable, Applicants will consider submitting a 37 C.F.R. 132 declaration to overcome the Examiner's rejection within the appropriate time frame.

Rejection of claims 17-20 under 35 U.S.C. § 103(a)

The Examiner has rejected claims 17-20 under 35 U.S.C. § 103(a), as being obvious over Nolan (WO 97/27,212) in view of Jia-Ping (Chinese Journal of Physical Medicine) or Ryan et al (Jrnl. of Immunological Methods). .). In particular, the Examiner is of the opinion that:

> Nolan discloses a method of screening for a bioactive agent capable of altering a cellular phenotype of a cell which comprises combining at least bioactive agent and a population of cell or introducing a library of nucleic acids encoding a candidate bioactive agents into a population of cells and sorting said cells in a FACS machine by separating said cells on the basis of at least three cellular parameters. Nolan further discloses other phenotypic changes of cells that can be sorted out based on these changes using FACS . . . Nolan does not disclose a method in which the cellular phenotype is exocytosis. However, Jia-ping discloses exocytosis a method of sorting cells by multi-parameter sorting technique using flow cytometry including exocytosis . . . Ryan

> discloses that gating on log 90 degree light scatter (e.g., exocytosis) and log red fluorescence reduced the incidence of nonspecific binding using multiple flow cytometric parameters. . . .

Applicants respectfully traverse the foregoing rejection. To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, *e.g., Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985). Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations (M.P.E.P. 2143).

Even if a combination of prior art references teaches or suggests all of the claim limitations, no *prima facie* case of obviousness may be established without a motivation to combine. *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art. *Id.* The level of skill in the art cannot be relied upon to provide the motivation to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

The Examiner has not set forth any motivation to combine these references and hence has not established a *prima facie* case of obviousness. Moreover, even if there were motivation to combine the references, the combination does not teach or suggest each and every element of the claims. The Examiner points out that Nolan discloses a method of screening for a bioactive

agent capable of altering a cellular phenotype of a cell which comprises combining at least bioactive agent and a population of cell or introducing a library of nucleic acids encoding a candidate bioactive agents into a population of cells and sorting said cells in a FACS machine by separating said cells on the basis of at least three cellular parameters. However, Applicants note that Nolan fails to disclose or suggest the use of *at least five parameters* in the FACS sorting protocol as required in the instantly claimed invention. Further, Nolan does not disclose or suggest exocytosis as one of the measurable cellular phenotypes.

Neither Jia-Ping nor Ryan cure the deficiency of the Nolan disclosure. Applicants acknowledge that Jia-Ping discloses the use of FACS, and specifically in relation to determining the cellular phenotype of exocytosis. Applicants acknowledge that Ryan discloses the use of FACS in connection with multiparameter sorting protocols. However, neither Jia-Ping or Ryan disclose or suggest the use of at least five parameters in the FACS sorting protocol. Jia-Ping, despite an initial statement that five parameters may be used, only discloses and enables four parameters: forward scattering, 90 scattering, fluorescence 1 and fluorescence 2. No fifth parameter is named or described. Ryan discloses only two parameters: log 90 scattering and red fluorescence. Further, there is no teaching or suggestion in either Jia-Ping or Ryan that their teachings be combined with the teachings of Nolan, e.g. that the cells of Nolan could be analyzed using the particular FACS protocols described in Jia-Ping and Ryan.

The combination of Nolan, Jia-Ping, and Ryan therefore fail to teach or suggest each and every aspect of the invention. Moreover, as set forth above, there would have been no motivation for one of skill in the art to combine the multiparameter FACS protocols for analyzing the exocytosis phenotype taught in Jia-Ping and Ryan with the teachings of Nolan, which does not even discuss exocytosis as a phenotype of interest. Accordingly, Applicants respectfully request withdrawal of the foregoing rejection.

Conclusion

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-832-1000

Respectfully submitted,

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